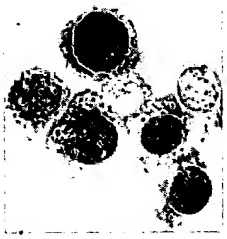
Cytochroma



Cancer Program

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CYP24 Inhibitors

Vitamin D has critical physiological roles in regulating calcium levels and cellular pro The active form of vitamin D, 1α,25-dihydroxyvitamin D3 (calcitriol) has emerged as differentiating/anti-proliferative agent for certain cell types.

Cytochroma is actively developing novel cancer therapeutics based on inhibiting the k cytochrome P450 enzyme that breaks down calcitriol (i.e. CYP24).

The challenge in administering vitamin D therapies is to deliver a sufficiently high dos effective without causing toxic side effects, such as hypercalciuria, hypercalcemia, or hyperphosphatemia. Due to the risks of these side effects, vitamin D therapies are cust administered at low dosages, which are at times ineffective. Starting dosages are incre cautiously, if at all, to minimize the chance of these toxic side effects, rather than to op therapeutic response. This information has led to the impetus to develop so-called "no vitamin D analogs in which the anti-proliferative properties of calcitriol might be sepa calcemic properties.

Cytochroma's unique approach to develop vitamin D analogues that are specific inhib CYP24, may provide effective treatments for cancer, where the therapeutic dose is not drug-induced hypercalcemia.

Cells overexpressing CYP24 escape the normal antiproliferative & prodifferentiating role of calcitriol. This may contribute to carcinogenesis.

CYP24 has recently been implicated as an oncogene. In breast cancer the CYP24 gene many fold resulting in a high level of CYP24 expression which may block control of t normally exerted by calcitriol. CYP24 activity has been observed to be present and up seven out of seven different continuous human prostatic carcinoma cell lines examine to inhibit the growth of these cell lines is inversely proportional to the level of CYP24 each cell line. In addition, two out of five non-small cell lung carcinoma cell lines hav to express high levels of CYP24. In non-small cell lung adenocarcinomas, CYP24 has identified as a gene that is over-expressed in patients with poor survival.

The therapeutic use of calcitriol and vitamin D analogs in cancer may therefore be lim refractoriness to therapy due to elevated CYP24 levels.

In addition, CYP24 is strongly induced in target cells by calcitriol. The therapeutic use

and vitamin D analogs in cancer may therefore also be limited by resistance to therapy develops over continued use.

Inducible expression of CYP24 limits the clinical response to vitamin D analog therapy.

Cytochroma is using its understanding of the critical calcitriol-regulating cytochrome l enzyme, CYP24, to identify drug candidates that manipulate and thereby control cellu proliferation. Cytochroma in collaboration with Johns Hopkins University, has discov proprietary vitamin D analogues that are specific and potent CYP24 inhibitors. These have been demonstrated in animal models to be non-calcemic or significantly less calc calcitriol. In addition, these compounds have been demonstrated to have strong antipr activity or to significantly enhance the antiproliferative activity of calcitriol in various lines.

Cytochroma has advanced 6 proprietary vitamin D analogues to preclinical developme treatment of cancer.

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